

U.S.S.N. 09/858,016

Filed: May 15, 2001

## AMENDMENT AND RESPONSE TO OFFICE ACTION

**In the claims**

1. (Twice amended) A pharmaceutical composition in unit dosage form for [both intraoral and] oral administration to a patient [, said unit dosage form configured to be placed within the mouth of said patient], which comprises:
  - (a) as a first portion, at least one discrete outer layer which dissolves or disintegrates[,], intraorally within about 10 minutes after contacting the patient's saliva, the layer comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level; and
  - (b) as a second portion located within said first portion outer layer, a therapeutically effective amount of at least one pharmaceutically active ingredient [capable of oral administration and] which is [releasable] released and orally ingestible by the patient after the outer layer has disintegrated or has dissolved intraorally.
2. The pharmaceutical composition defined in claim 1 in the form of a tablet or capsule.
3. The pharmaceutical composition defined in claim 2 wherein the unit dosage form is a tablet and the second portion of the composition is an inner core or at least one layer of a multi-layer tablet, and the first portion is either an outer coating applied on the core or is one or more of the outer layers of a multi-layer tablet.
4. (amended) The pharmaceutical composition defined in claim 2 wherein the unit dosage form is a capsule and the second portion of the composition is an uncoated capsule including the pharmaceutically active ingredient capable of sublingual or buccal

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

absorption in a therapeutically effective level on which the first portion is applied as an outer layer forming an outer coating.

5. The pharmaceutical composition defined in claim 3 wherein the outer coating is a film coat that is applied as a layer to the inner core.
6. The pharmaceutical composition defined in claim 3 wherein the outer coating is a compression coat that is compressed around the inner core.
7. (amended) The pharmaceutical composition defined in claim 5 wherein the film coat comprises the at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and at least one pharmaceutically acceptable coating polymer selected from the group consisting of cellulose, hydroxypropyl methylcellulose, methyl cellulose, polyvinylpyrrolidone, and polyethylene glycol, a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable glidant and a pharmaceutically acceptable colorant.
8. (amended) The pharmaceutical composition defined in claim 6 wherein the compression coat comprises the at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and at least one pharmaceutically acceptable excipient for intraoral administration of the pharmaceutically active ingredient.
9. (amended) The pharmaceutical composition defined in claim 6 wherein the compression coat comprises the at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level formulated in a pharmaceutically acceptable effervescent agent which generates effervescence when contacted with salivary fluid.

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

10. (amended) The pharmaceutical composition defined in claim 3 wherein the first portion comprises one or two outer layers each comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and one or more pharmaceutically acceptable excipients for intraoral administration of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level.
11. (amended) The pharmaceutical composition defined in claim 3 wherein the outer layer of the multi-layer tablet is formulated with a pharmaceutically acceptable effervescent agent which generates effervescence when contacted with salivary fluid.
12. The pharmaceutical composition defined in claim 7 wherein the film coat further comprises a pharmaceutically acceptable flavoring agent.
13. (amended) The pharmaceutical composition defined in claim 3 wherein the inner core is an immediate drug release tablet comprising the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and at least one pharmaceutically acceptable excipients for oral administration of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level.
14. (amended) The pharmaceutical composition defined in claim 3 wherein the inner core is in a configuration which provides sustained release of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and which further provides an immediate drug release layer tablet comprising the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and at least one pharmaceutically acceptable excipient for

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

oral administration of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level.

15. (amended) The pharmaceutical composition defined in claim 3 wherein the second portion is the at least one layer of the multi-layer tablet comprising the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and which is an immediate drug release layer.
16. (amended) The pharmaceutical composition defined in claim 3 wherein the second portion is the at least one inner layer and provides sustained release of the pharmaceutically active ingredient suitable for sublingual or buccal absorption in a therapeutically effective level over a period of 0.5 to 24 hours.
17. (amended) The pharmaceutical composition defined in claim 3 wherein a delayed release coating covers the inner core and comprises the second portion of the composition and then the first portion of the composition is an outer layer over the delayed release coating to delay release of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level for a period of 0.5 to 12 hours.
18. The pharmaceutical composition defined in claim 17 wherein the delayed release coating comprises one or more pharmaceutically acceptable polymer selected from the group consisting of methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose acetate succinate, ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, cellulose acetate trimellitate, carboxymethylcellulose sodium, acrylic acid polymers and copolymers, polymers or copolymers of methacrylic acid, methyl acrylate, ethyl acrylate,

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

methyl methacrylate, ethyl methacrylate, vinyl acetate, vinyl acetate phthalate, or an azo compound, polyvinyl pyrrolidone, pectin, amylase, shellac, zein, and guar gum.

19. The pharmaceutical composition defined in claim 3 wherein the inner core or a layer of the multi-layer table core is chewable and comprises at least one pharmaceutically acceptable excipient suitable for a chewable medication and a flavoring agent.
20. The pharmaceutical composition defined in claim 4 wherein the film coat comprises the pharmaceutically active ingredient capable of intraoral administration and at least one pharmaceutically acceptable coating polymer selected from the group consisting of cellulose, hydroxypropyl methylcellulose, methyl cellulose, polyvinyl pyrrolidone, and polyethylene glycol, a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable glidant, a pharmaceutically acceptable colorant, and optionally a pharmaceutically acceptable flavoring agent.
21. (amended) The pharmaceutical composition defined in claim 4 wherein the second portion of the composition is a capsule containing the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level and a pharmaceutically acceptable excipient for sustained release of the pharmaceutically active ingredient suitable for sublingual or buccal absorption in a therapeutically effective level to provide a sustained release effect of the pharmaceutically active ingredient for 0.5 to 24 hours.
22. (amended) The pharmaceutical composition defined in claim 1 wherein the outer layer disintegrates or dissolves within 10 minutes, when the composition is contacted with saliva during intraoral administration.

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

23. (amended) The pharmaceutical composition defined in claim 22 wherein the second part of the composition containing the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level remains intact until the intraoral administration of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level has been completed.
24. (amended) The pharmaceutical composition defined in claim 22 wherein the outer layer disintegrates immediately to allow a rapid intraoral mucosal absorption of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level released from the outer layer.
25. (amended) The pharmaceutical composition defined in claim 1 which further comprises a pharmaceutically acceptable signaling system located between the first portion and second portion of the composition, within the first portion of the composition or within the second portion of the composition and that is detectable by the patient upon substantial release of the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level during intraoral administration thereby informing the patient that it is time to chew or swallow the remaining second part of the composition containing the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level.
26. (amended) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level is metabolized in a first pass which is avoided by intraoral administration.

U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

27. (amended) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level has a rapid onset of desired therapeutic effect through sublingual or buccal absorption.
28. (amended) The pharmaceutical composition defined in claim 1 wherein the pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level is selected from the group consisting of analgesics, antihistamines, antidiarrheals, anxiolytics, hypnotics, stimulants, cardiovascular drugs, pulmonary drugs, anti-hypertensives, anti-emetics, anti-inflammatory drugs, renal drugs, steroids, drugs for neurological disorders, anti-psychotic drugs, drugs for treating endocrine disorders, drugs for promoting immunology, drugs for treating osteoarthritis, drugs for treating glaucoma, drugs for treating allergic rhinitis, drugs for treating anemias and other hematological disorders, drugs for treating infectious diseases, drugs for the treatment and symptoms of cancer, drugs for insomnia, and antidiabetic drugs.
29. (Twice amended) A process for the preparation of a pharmaceutical composition in unit dosage form as a tablet or capsule for both intraoral and oral administration to a patient[, said pharmaceutical composition placed within the mouth of said patient], which comprises:
- (a) as a first portion, at least one discrete outer layer which dissolves or disintegrates, intraorally, within about 10 minutes after contacting the patient's saliva, the layer comprising a therapeutically effective amount of at least one pharmaceutically active ingredient capable of sublingual or buccal absorption in a therapeutically effective level; and

U.S.S.N. 09/858,016

Filed: May 15, 2001

## AMENDMENT AND RESPONSE TO OFFICE ACTION

(b) as a second portion located within said first portion outer layer, a therapeutically effective amount of at least one pharmaceutically active ingredient capable of oral administration and which is releasable and orally ingestible by the patient after the at least one outer layer has disintegrated or has dissolved within the patient's mouth which comprises the steps of:

(i) providing the second portion as an inner tablet core or as at least one layer of a multi-layer tablet core or as an uncoated capsule; and

(ii) applying the first portion as an outer layer or as several outer layers forming an outer coating on the first portion.

30. (cancelled)

31. (cancelled)

32. (Twice amended) An analgesic pharmaceutical composition in unit dosage form as a tablet for both intraoral and oral administration to a patient, [said unit dosage form configured to be placed within the mouth of said patient and has an outer coating which disintegrates or dissolves in the patient's mouth,] which comprises:

(a) as a first portion, or at least one discrete outer layer which dissolves or disintegrates within about 10 minutes after contacting the patient's saliva, intraorally, the layer comprising a therapeutically effective amount of butorphanol tartrate capable of sublingual or buccal absorption in a therapeutically effective level;

(b) as a second portion located within said first portion, a therapeutically effective amount of rofecoxib capable of oral administration and which is releasable and orally ingestible by the patient after the outer layer has disintegrated or has dissolved intraorally; and



U.S.S.N. 09/858,016

Filed: May 15, 2001

**AMENDMENT AND RESPONSE TO OFFICE ACTION**

(c) a pharmaceutically acceptable signaling system located between the first portion and second portion of the composition, within the first portion of the composition or within the second portion of the composition and that is detectable by the patient upon substantial release of the butorphanol tartrate capable of intraoral administration during intraoral administration thereby informing the patient that it is time to orally ingest the remaining second part of the composition containing the rofecoxib capable of oral administration.